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PTO/SB/16 (08-03)

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
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☐ *Additional inventors are being named on the separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

PRACTICAL, COST-EFFECTIVE SYNTHESIS OF COQ10

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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OR

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* 25 ☐ CD(s), Number

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☒ Application Data Sheet. See 37 CFR 1.76

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☒ Applicant claims small entity status. See 37 CFR 1.27.

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80

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: .

Respectfully submitted,

SIGNATURE

Date 12/05/03

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Attorney Docket No.: 2307Z-110620US

PROVISIONAL

PATENT APPLICATION

PRACTICAL, COST-EFFECTIVE SYNTHESIS OF CoQ_{10}

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AS FILED IN THE USPTO—DECEMBER 5, 2003

PRACTICAL, COST-EFFECTIVE SYNTHESIS OF CoQ_{10}

BACKGROUND OF THE INVENTION

The ubiquinones, also commonly called coenzyme Q_n (n = 1-12), constitute essential cellular components of many life forms. In humans, CoQ_{10} is the predominant member of this class of polyprenoidal natural products and is well-known to function primarily as a redox carrier in the respiratory chain (Lenaz, COENZYME Q. BIOCHEMISTRY, BIOENERGETICS, AND CLINICAL APPLICATIONS OF UBIQUINONE, Wiley-Interscience: New York (1985); Trumpower, FUNCTION OF UBIQUINONES IN ENERGY CONSERVING SYSTEMS, Academic Press, New York (1982); Thomson, R. H., NATURALLY OCCURRING QUINONES, 3rd ed., Academic Press, New York (1987); Bliznakov *et al.*, THE MIRACLE NUTRIENT COENZYME Q_{10}, Bantom Books, New York (1987)).

Coenzyme Q plays an essential role in the orchestration of electron-transfer processes necessary for respiration. Almost all vertebrates rely on one or more forms of this series of compounds which are found in the mitrochondria of every cell (*i.e.*, they are ubiquitous, hence the alternative name "ubiquinones"). Although usually occurring with up to 12 prenoidal units attached to a *p*-quinone headgroup, CoQ_{10} is the compound used by humans as a redox carrier. Oftentimes unappreciated is the fact that when less than normal levels are present, the body must construct its CoQ_{10} from lower forms obtained through the diet, and that at some point in everyone's life span the efficiency of that machinery begins to drop. (Blizakov *et al.*, *supra*) The consequences of this *in vivo* deterioration can be substantial; levels of CoQ_{10} have been correlated with increased sensitivity to infection (*i.e.*, a weakening of the immune system), strength of heart muscle, and metabolic rates tied to energy levels and vigor. In some countries (*e.g.*, Japan), CoQ_{10} is treated as a "drug", prescribed especially for those having suffered from heart disease, and is among the leading pharmaceuticals sold. In the United States, however, it is considered a dietary supplement, sold typically in health food stores or through mail order houses at reasonable prices. It is indeed fortunate that quantities of CoQ_{10} are available via well-established fermentation and extraction processes (*e.g.*, Sasikala *et al.*, *Adv. Appl. Microbiol.*, **41**:173 (1995); U.S. Patent No. 4,447,362; 3,313,831; and 3,313,826) an apparently more cost-efficient route relative to total synthesis. However, for producing lower forms of CoQ, such processes are either far less efficient or are unknown. Thus, the costs of these materials for research purposes are

astonishingly high, *e.g.*, CoQ_6 is ~$22,000/g, and CoQ_9 is over $40,000/g. (Sigma-Aldrich Catalog, Sigma-Aldrich: St. Louis, pp. 306-307 (1998)).

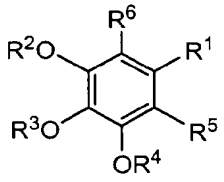
Several approaches to synthesizing the ubiquinones have been developed over the past 3-4 decades, attesting to the importance of these compounds. Recent contributions have invoked such varied approaches as Lewis acid-induced prenoidal stannane additions to quinones, (Naruta, *J. Org. Chem.*, **45**:4097 (1980)) reiterative Pd(0)-catalyzed couplings of doubly activated prenoidal chains with allylic carbonates bearing the required aromatic nucleus in protected form (Eren *et al.*, *J. Am. Chem. Soc.*, **110**:4356 (1988) and references therein), and a Diels—Alder, retro Diels—Alder route to arrive at the quinone oxidation state directly (Van Lient *et al.*, *Rec. Trav. Chim. Pays-Bays* **113**:153 (1994); and Rüttiman *et al.*, *Helv. Chim. Acta*, **73**:790 (1990)). Nonetheless, all are lengthy, linear rather than convergent, and/or inefficient. Moreover, problems in controlling double bond stereochemistry using, *e.g.*, a copper(I)-catalyzed allylic Grignard-allylic halide coupling can lead to complicated mixtures of geometrical isomers that are difficult to separate given the hydrocarbon nature of the side chains (Yanagisawa, *et al.*, *Synthesis*, 1130 (1991)).

For the reasons set forth above, a convergent method for the synthesis of the ubiquinones and their analogues which originates with a simple benzenoid precursor and procedes with retention of the double bond stereochemistry would represent a significant advance in the synthesis of ubiquinones and their analogues. The present invention provides such a method and ubiquinone precursors of use in the method.

SUMMARY OF THE INVENTION

The present invention provides an efficient and inexpensive method for preparing ubiquinones and structural analogues of these essential molecules. Also provided are new compounds that are structurally simple and provide a convenient, efficient and inexpensive entry into the method of the invention.

Thus, in a first aspect, the present invention provides a compound according to Formula I:

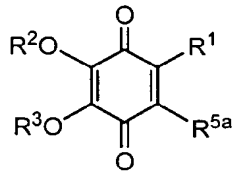


(I).

In Formula I, R^1, R^2 and R^3 are independently selected substituted or unsubstituted C_1-C_6 alkyl groups, preferably methyl groups. R^4 represents H, substituted or unsubstituted alkyl, preferably methyl, or a protecting group. R^5 is selected from–C(O)H, and $-CH_2Y$, in which Y is OR^7, SR^7, NR^7R^8, or a leaving group. R^7 and R^8 are independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl. R^6 is H or -OC(O)H, or another group that is readily converted to a quinone ketone moiety or a phenyl H atom.

In an exemplary embodiment, when R^5 is -CH(O) or Y is a leaving group, e.g., halo, then R^6 is OC(OH).

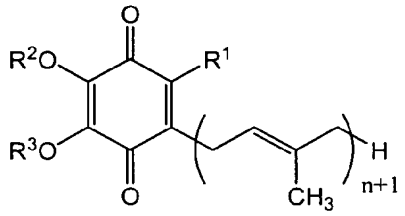
In a second aspect, the invention provides compounds according to Formula Ia:



(Ia)

in which R^1, R^2 and R^3 are as described for Formula I and R^{5a} is -C(O)H or CH_2OR^{7a} in which R^{7a} is H or substituted or unsubstituted alkyl.

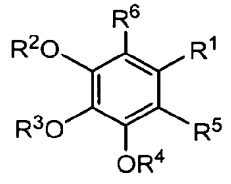
In a third aspect, the present invention provides a method for preparing a compound according to Formula V:



(V).

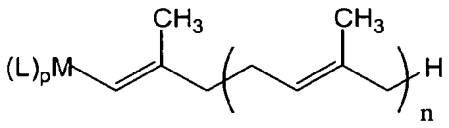
In Formula V, each of R^1, R^2 and R^3 are substituents as described for Formula I, and the subscript n represents an integer from 0 to 20.

The method of the invention comprises, contacting a compound according to Formula I:



(I)

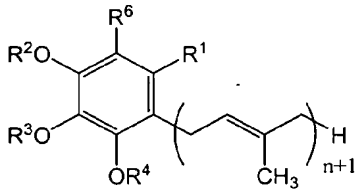
with a compound according to Formula II:



(II)

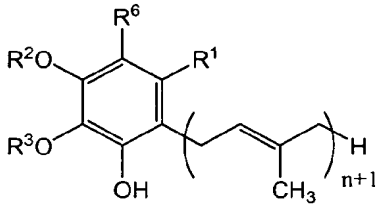
in which L is an organometallic ligand; M is a metal; p is an integer from 1 to 5; and n is an integer from 0 to 20. Each of the organometallic ligands, L, can be the same or different. R^1-R^6 are as discussed above.

The mixture of compounds according to Formulae I and II are contacted with a catalyst that is effective at catalyzing coupling between a benzylic carbon atom, such as that in Formula I and an organometallic species according to Formula II. The coupling of the compounds of Formulae I and II, forms a compound according to Formula III:



(III).

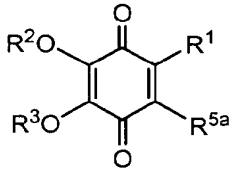
R^4 is preferably removed from the compound according to Formula III to produce a compound according to Formula IV:



(IV).

Contacting the compound according to Formula IV with an oxidant yields quinone V.

In another aspect, the invention provides a method for preparing the alkylated quinone of the invention by direct alkylation of a benzyl ether precursor of the quinone. Thus, a compound according to Formula VI:



(VI)

is contacted with a compound according to Formula II in the presence of a catalyst. An exemplary catalyst is a nickel catalyst.

Other objects and advantages of the invention will be apparent to those of skill in the art from the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a representative synthetic scheme for the process of the invention.

DETAILED DESCRIPTION OF THE INVENTION AND THE PREFERRED EMBODIMENTS

Definitions

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multi-valent radicals, having the number of carbon atoms designated *(i.e.* C_1-C_{10} means one to ten carbons). Examples of saturated hydrocarbon radicals include groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)ethyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. The term "alkyl," unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below as "heteroalkyl," "cycloalkyl" and "alkylene." The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

The terms "alkoxy," "alkylamino" and "alkylthio" refer to those groups having an alkyl group attached to the remainder of the molecule through an oxygen, nitrogen or sulfur atom, respectively. Similarly, the term "dialkylamino" is used in a conventional sense to refer to –NR'R'' wherein the R groups can be the same or different alkyl groups.

The term "acyl" or "alkanoyl" by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and an acyl radical on at least one terminus of the alkane radical.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. Examples include $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, and $-CH=CH-N(CH_3)-CH_3$. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. Also included in the term "heteroalkyl" are those radicals described in more detail below as "heteroalkylene" and "heterocycloalkyl." The term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by $-CH_2-CH_2-S-CH_2CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini. Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include 1 -(1,2,5,6-tetrahydropyridyl), 1 -piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

Additionally, terms such as "fluoroalkyl," are meant to include monofluoroalkyl and polyfluoroalkyl.

The term "aryl," employed alone or in combination with other terms *(e.g.,* aryloxy, arylthioxy, arylalkyl) means, unless otherwise stated, an aromatic substituent which can be a single ring or multiple rings (up to three rings), which are fused together or linked covalently. "Heteroaryl" are those aryl groups having at least one heteroatom ring member. Typically, the rings each contain from zero to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. The "heteroaryl" groups can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl ring systems are selected from the group of acceptable substituents described below. The term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.,* benzyl, phenethyl, pyridylmethyl and the like) or a heteroalkyl group (*e.g.,* phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

Each of the above terms (*e.g.,* "alkyl," "heteroalkyl" and "aryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be a variety of groups selected from, for example: -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO_2R', CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -NH-$C(NH_2)$=NH, -NR'$C(NH_2)$=NH, -NH-$C(NH_2)$=NR', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -CN and -NO_2 in a number ranging from zero to (2N+ 1), where N is the total number of carbon atoms in such radical. R', R" and R"' each independently refer to hydrogen, unsubstituted (C_1-C_8)alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted alkyl,

alkoxy or thioalkoxy groups, or aryl-(C_1-C_4)alkyl groups. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups such as haloalkyl (*e.g.*, -CF_3 and -CH_2CF_3) and acyl (e.g., -$C(O)CH_3$, -$C(O)CF_3$, -$C(O)CH_2OCH_3$, and the like).

Similarly, substituents for the aryl groups are varied and are selected from: -halogen, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, -NO_2, -CO_2R', -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', -NR"$C(O)_2$R', -NR'-C(O)NR"R"', -NH-$C(NH_2)$=NH, -NR'$C(NH_2)$=NH, -NH-$C(NH_2)$=NR', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -N_3, -$CH(Ph)_2$, perfluoro(C_1-C_4)alkoxy, and perfluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R" and R"' are independently selected from hydrogen, (C_1-C_8)alkyl and heteroalkyl, unsubstituted aryl, (unsubstituted aryl)-(C_1-C_4)alkyl, (unsubstituted aryl)oxy-(C_1-C_4)alkyl and perfluoro(C_1-C_4)alkyl.

Two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula –T-C(O)-$(CH_2)_q$-U-, wherein T and U are independently -NH-, -O-, -CH_2- or a single bond, and the subscript q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CH_2-, -O-, -NH-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -$(CH_2)_s$-X-$(CH_2)_t$-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituent R' in -NR'- and -$S(O)_2$NR'- is selected from hydrogen or unsubstituted (C_1-C_6)alkyl.

As used herein, the term "heteroatom" is meant to include, for example, oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present invention.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

As used herein, the term "leaving group" refers to a portion of a substrate that is cleaved from the substrate in a reaction.

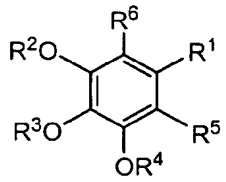
"Protecting group," as used herein refers to a portion of a substrate that is substantially stable under a particular reaction condition, but which is cleaved from the substrate under a different reaction condition. A protecting group can also be selected such that it participates in the direct oxidation of the aromatic ring component of the compounds of the invention. For examples of useful protecting groups, *see*, for example, Greene *et al.*, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, John Wiley & Sons, New York, 1991.

Introduction

The present invention provides an efficient and cost-effective route to the ubiquinones and their analogues. The present method is quite general and can be used to afford precursors, and direct access, to CoQ_n and analogues as well as systems found in vitamins K_1 and K_2 and their analogues. The invention also provides compounds that are useful in the method of the invention.

The Compounds

Thus, in a first aspect, the present invention provides a compound according to Formula I:



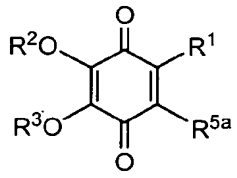
(I).

In Formula I, R^1, R^2 and R^3 are independently selected substituted or unsubstituted C_1-C_6 alkyl groups, preferably methyl groups. R^4 represents H, substituted or unsubstituted alkyl, preferably methyl, or a protecting group. R^5 is selected from–C(O)H, and $–CH_2Y$, in which Y is OR^7, SR^7, NR^7R^8, or a leaving group. R^7 and R^8 are independently selected

from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl. R^6 is H, OH or -OCH(O), or another group that is readily converted to a quinone ketone moiety or a phenyl H atom.

In an exemplary embodiment, when R^5 is -CH(O) or Y is a leaving group, e.g., halo, then R^6 is OC(OH).

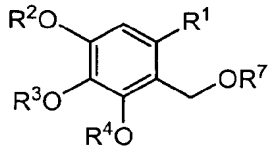
In a second aspect, the invention provides compounds according to Formula Ia:



(Ia)

in which R^1, R^2 and R^3 are as described for Formula I and R^{5a} is -C(O)H or CH_2OR^{7a} in which R^{7a} is H or substituted or unsubstituted alkyl.

Exemplary compounds of the invention according to Formulae I and Ia include: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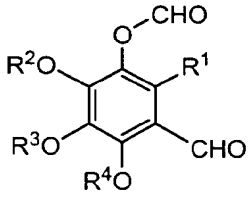
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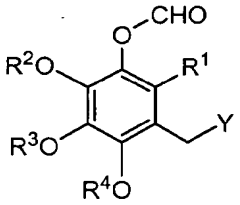
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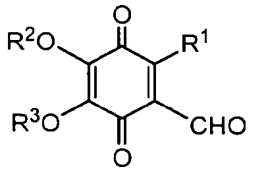
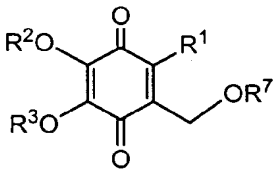
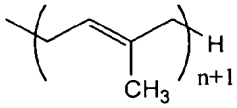

; and


in which the identity of the substituents is as discussed hereinabove.

In still further exemplary compounds according to the invention, R^1, R^2, and R^3 are methyl; and R^4 is methyl or H.

In another exemplary embodiment R^5 and R^{5a} have the structure according to Formula II:



(II)

In Formula II, n is a member selected from the integers from 0 to 20, and preferably from 0 to 13 and more preferably from 4 to 10.

Synthesis

The compounds of the invention are synthesized by an appropriate combination of generally well-known synthetic methods. Techniques useful in synthesizing the compounds of the invention are both readily apparent and accessible to those of skill in the relevant art. The discussion below is offered to illustrate certain of the diverse methods available for use in assembling the compounds of the invention, it is not intended to define the scope of reactions or reaction sequences that are useful in preparing the compounds of the present invention.

The compounds of the invention are prepared by art-recognized methods or modifications thereof. For example, The synthesis of quinones functionalized with a halomethyl group can be accomplished using methods such as that described by Lipshutz *et al., J. Am. Chem. Soc.* **121**: 11664-11673 (1999)), the disclosure of which is incorporated herein by reference.

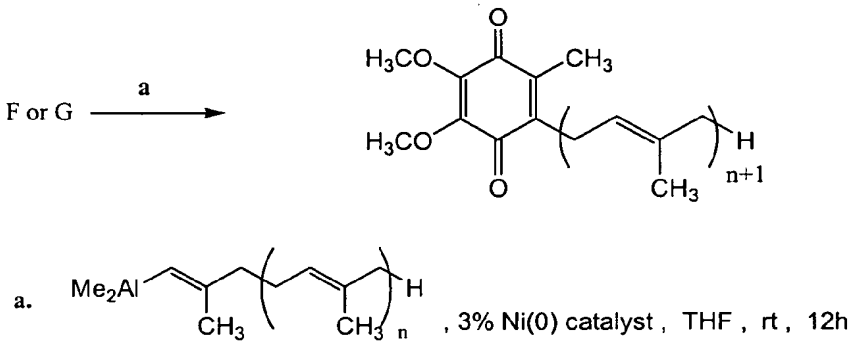
A representative synthetic scheme setting forth the preparation of selected compounds of the invention is displayed below in **FIG 1**. In **FIG. 1**, commercially available A is formylated, yielding aldehyde B. The aldehyde is demethylated, affording phenol C, the aldehyde group of which is reduced to benzyl alcohol D.

A wide array of art-recognized reducing agents can be used to effect the transformation of the aldehyde C to the alcohol of D. *See*, for example, Trost BM, *et al.*, COMPREHENSIVE ORGANIC SYNTHESIS: REDUCTION, Pergamon Press, 1992. In a presently preferred embodiment, the reducing agent is a reagent that is a source of hydrogen which is a member selected from the group consisting of metal hydrides, and catalytic hydrogenation. In another preferred embodiment, the reduction is an electrochemical reduction.

By contacting D with an oxidant, it is readily converted to the corresponding quinone E. The benzylic alcohol moiety of E is contacted with a halogenating agent, such as thionyl chloride, affording benzyl halide F, which can be directly coupled to a vinyl alane according to the procedure of Negishi et al., *Org. Lett.* **4**: 261 (2002). Alternatively, the alcohol moiety of E is alkylated, giving quinone ether G.

Rather than being oxidized to the corresponding quinone, D can be readily converted to benzylic ether H by contacting it with an alkylating agent. The benzylic ether is oxidized to quinone G. The ether moiety is replaced with a vinyl alane, by coupling the quinone-linked ether carbon atom with an activated analogue of compound II, for example, the vinyl alane of Scheme 1, below.

A representative scheme for preparing a ubiquinone, starting with quinone F or G is set forth in Scheme 1.



Scheme 1

In Scheme 1, the chloromethyl quinone F or the benzyl ether quinone G is contacted with a vinylalane in the presence of a Ni(0) catalyst. The vinyl moiety and the carbon at the benzylic position couple, affording the corresponding ubiquinone.

In each of the reaction pathways described above, purification of the end-products and the intermediates, where necessary, is accomplished by substantially any means known in the art including, for example, precipitation, crystallization and chromatography (*e.g.*, TLC, column, flash, HPLC) or a combination thereof.

The synthetic schemes set forth herein (**FIG. 1** and Scheme 1) are intended to be exemplary of the synthesis of one compound of the invention. Those of skill in the art will recognize that many other synthetic strategies leading to compounds within the scope of the present invention are available. For example, by a slight modification of the starting material above, a compound having ethoxy, rather than methoxy groups is produced. Moreover, both the leaving and protecting groups shown in Scheme 1 can be replaced with other useful groups.

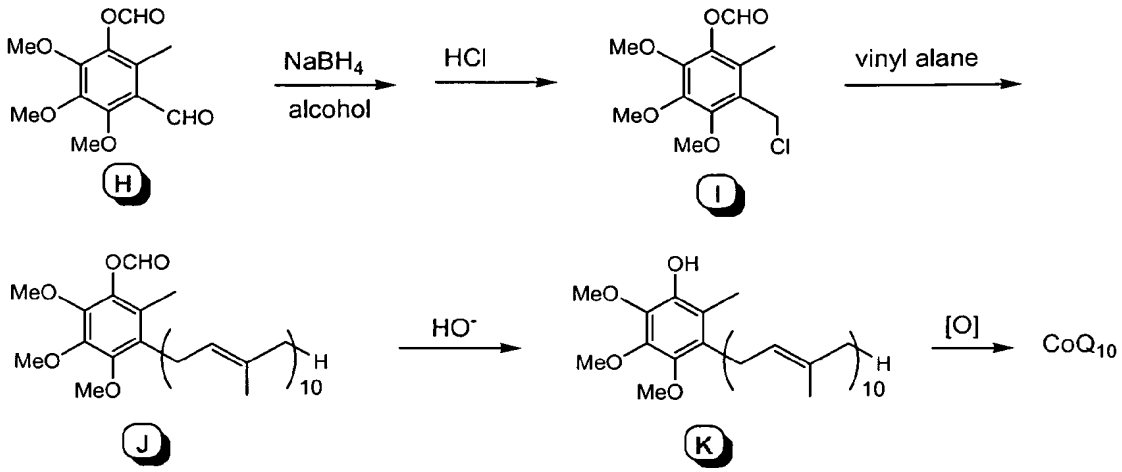
The reaction pathways set forth in **FIG. 1** and Scheme 1 can be altered by using a leaving group other than a chloro at the methylene of F. Useful leaving groups include, but are not limited to, other halides, sulfonic esters, oxonium ions, alkyl perchlorates, ammonioalkanesulfonate esters, carboxylic acid esters, carbonates, alkylfluorosulfonates, ethers, and fluorinated compounds (*e.g.*, triflates, nonaflates, tresylates) and the like. The choice of these and other leaving groups appropriate for a particular set of reaction conditions is within the abilities of those of skill in the art (*see*, for example, March J, ADVANCED ORGANIC CHEMISTRY, 2nd Edition, John Wiley and Sons, 1992; Sandler SR, Karo W, ORGANIC FUNCTIONAL GROUP PREPARATIONS, 2nd

Edition, Academic Press, Inc., 1983; and Wade LG, COMPENDIUM OF ORGANIC SYNTHETIC METHODS, John Wiley and Sons, 1980).

In a presently preferred embodiment, the leaving group, Y, is a halogen, more preferably, a chloro group.

Moreover, the methyl group used to protect the phenol oxygen atom in Scheme 1 and **FIG. 1** can be replaced with a number of other art-recognized protecting groups. Useful phenol protecting groups include, but are not limited to, ethers formed between the phenol oxygen atom and substituted or unsubstituted alkyl groups (*e.g.*, sulfonic acid esters, methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, methylthiomethyl, phenylthiomethyl, 2,2-dichloro-1,1-difluoroethyl, tetrahydropyranyl, phenacyl, p-bromophenacyl, cyclopropylmethyl, allyl, isopropyl, cyclohexyl, t-butyl, benzyl, 2,6-dimethylbenzyl, 4-methoxybenzyl, o-nitrobenzyl, 2,6-dichlorobenzyl, 4-(dimethylaminocarbonyl)benzyl, 9-anthrymethyl, 4-picolyl, heptafluoro-p-tolyl, tetrafluoro-4-pyridyl); silyl ethers (*e.g.*, trimethylsilyl, t-butyldimethylsilyl); esters (*e.g.*, acetate, levulinate, pivaloate, benzoate, 9-fluorenecarboxylate); carbonates (*e.g.*, methyl, 2,2,2-trichloroethyl, vinyl, benzyl); phosphinates (*e.g.*, dimethylphosphinyl, dimethylthiophosphinyl); sulfonates (*e.g.*, methanesulfonate, toluenesulfonate, 2-formylbenzenesulfonate), and the like (*see, e.g.*, Greene *et al.*, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, John Wiley & Sons, New York, 1991).

In another exemplary embodiment, the compound of the invention includes a OC(O)H moiety as the R^6 substituent. As shown in Scheme 2, the OC(O)H moiety is a protecting group that remains intact during the conversion of the aldehyde of H to the chloromethyl group of I, and its alkylation to produce J. The OC(O)H group is removed by hydrolytic cleavage and the resulting hydroxyl derivative K is readily oxidized to the corresponding ubiquinone.

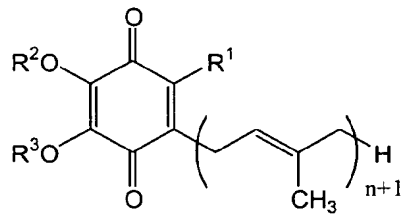


Scheme 2

The Methods

In one aspect, the method of the present invention is based on a retrosynthetic disconnection that relies on the well-known maintenance of olefin geometry in group 10 coupling reactions (Hegedus, TRANSITION METALS IN THE SYNTHESIS OF COMPLEX ORGANIC MOLECULES, University Science Books, Mill Valley, CA, 1994). The discussion that follows focuses on a reaction, in which the coupling partners are a vinyl organometallic and a species with a benzylic position having a leaving group thereon. The focus of the discussion is for clarity of illustration, and other methods and coupling partners appropriate for use in those methods will be apparent to those of skill in the art and are within the scope of the present invention.

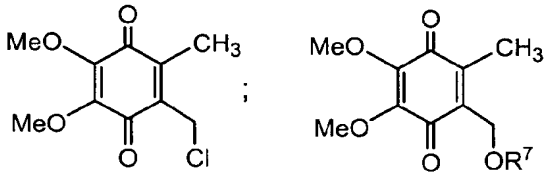
Thus, the present invention provides a method for preparing a compound according to Formula III:



(III).

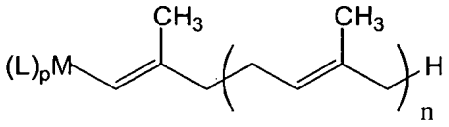
In Formula III, each of R^1, R^2, R^3 and n is as described above.

Referring to **FIG. 1** and Scheme 1, the method of the invention comprises, contacting compound F or G:



F G

in which the substituents are as discussed above, with a compound according to Formula IV:



(IV).

In Formula IV, L is an organometallic ligand; M is a metal ion; p is an integer from 1 to 5; and n is an integer from 0 to 13. Each of the organometallic ligands, L, can be the same or different.

Compounds F or G and a compound according to Formula IV are contacted in the presence of a catalyst that is effective at catalyzing the coupling of a benzylic carbon atom, such as that in compounds F and G and an organometallic species according to Formula IV. The coupling of compound F or G with a compound according to Formula IV affords the compound according to Formula III.

As shown in Scheme 2, the invention provides another exemplary embodiment, the invention provides a further method for preparing a compound according to Formula III.

The ubiquinones and their analogues include an alkene unit, which in the higher homologues (*i.e.*, $n \geq 2$) repeats in a precise and predictable manner. The method of the invention is appropriate for synthesizing a ubiquinone or ubiquinone analogue having an alkene component that repeats as many times as is desired. In a presently preferred embodiment n is an integer from 0 to 20, more preferably from 4 to 10.

The metals, M, of use in the method of the invention include those metals that can carbometalate the alkyne component of the reaction pathway to produce a species according to Formula IV. Presently preferred metals include transition metals and aluminum, of which aluminum is presently preferred. The metal can be formally neutral or it can be charged (*e.g.* an aluminate). The transition metal chemistry can be catalytic or stoichiometric. For example, the alkyne can be metalated by catalytic carbocupration

using Cu(I) to form an adduct that is used directly to form a ubiquinone or is subsequently transmetalated to the corresponding zinc reagent.

The coordination number of M is satisfied by the bonding or coordination to the metal ion of the requisite number of organometallic ligands, such as Lewis base donors (*e.g.*, halogen donors, oxygen donors, mercaptide ligands, nitrogen donors, phosphorous donors, and heteroaryl groups); hydrides; carbon ligands bound principally by σ-bonds (*e.g.*, alkyls, aryls, vinyls, acyl and related ligands); carbon ligands bound by σ- and π-bonds (*e.g.*, carbonyl complexes, thiocarbonyl, selenocarbonyl, tellurocarbonyl, carbenes, carbynes, σ-bonded aetylides, cyanide complexes, and isocyanide complexes); ligands bound through more than one atom (*e.g.*, olefin complexes, ketone complexes, acetylene complexes, arene complexes, cyclopentadienyl complexes, π-allyl complexes); unsaturated nitrogen ligands (*e.g.*, macrocyclic imines, dinitrogen complexes, nitric oxide complexes, diazonium complexes); and dioxygen complexes. Other useful combinations of metal ions and ligands will be apparent to those of skill in the art. *See*, for example, Collman JP *et al.* PRINCIPLES AND APPLICATIONS OF ORGANOTRANSITION METAL CHEMISTRY, University Science Books, 1987.

In another preferred embodiment, the catalysis of the coupling utilizes a species that comprises a transition metal. Exemplary transition metal species of use as catalysts include, but are not limited to, Cu(I), Pd(0), Co(0) and Ni(0). Recent reports have demonstrated that couplings, using the appropriate reaction partners and based on metal catalysis, are quite general and can be used to directly afford known precursors (Naruta, *J. Org. Chem.*, **45**:4097 (1980); Eren, *et al.*, *J. Am. Chem. Soc.*, **110**:4356 (1988) and references therein; Van Lient *et al.*, *Rec. Trav. Chim. Pays-Bays* **113**:153 (1994); Rüttiman *et al.*, *Helv. Chim. Acta*, **73**:790 (1990); Terao *et al.*, *J. Chem. Soc., Perkin Trans.* **1**:1101 (1978), Lipshutz *et al., J. Am. Chem. Soc.* **121**: 11664-11673 (1999); Lipshutz *et al., J. Am. Chem. Soc.* **118**: 5512-5313 (1999)). In a preferred embodiment, the metal is Ni(0).

The catalyst can be formed by any of a variety of methods recognized in the art. In a preferred embodiment, in which the transition metal is Ni(0), the catalyst is formed by a method comprising, contacting $NiCl_2(PPh_3)_2$, or a similar Ni species, with about two equivalents of a reducing agent (*e.g.*, n-butyllithium), thereby reducing said $NiCl_2(PPh_3)_2$ to Ni(0). Alternatively, other readily available forms of Ni(0) can be employed (*e.g.*, $Ni(COD)_2$).

The method of the invention is practiced with any useful amount of catalyst. In a preferred embodiment, the catalyst is present in an amount from about 0.1 mole % to about 10 mole %, more preferably from about 2 mole % to about 5 mole %.

The catalyst can be a homogeneous or heterogeneous catalyst (Cornils B, Herrmann WA, APPLIED HOMOGENEOUS CATALYSIS WITH ORGANOMETALLIC COMPOUNDS: A COMPREHENSIVE HANDBOOK IN TWO VOLUMES, John Wiley and Sons, 1996; Clark JH, CATALYSIS OF ORGANIC REACTIONS BY SUPPORTED INORGANIC REAGENTS, VCH Publishers, 1994; Stiles AB, CATALYST SUPPORTS AND SUPPORTED CATALYSTS: THEORETICAL AND APPLIED CONCEPTS, Butterworth-Heinemann, 1987). In one preferred embodiment, the catalyst is supported on a solid material (*e.g.*, charcoal, silica, *etc.*). In another preferred embodiment, the catalyst is a supported nickel catalyst (*see, e.g.*, Lipshutz *et al.*, *Tetrahedron* **56**:2139-2144 (2000); Lipshutz and Blomgren, *J. Am. Chem. Soc.* **121**: 5819-5820 (1999); and Lipshutz *et al.*, *Inorganica Chimica Acta* **296**: 164-169 (1999).

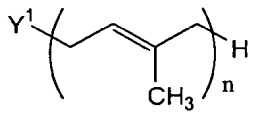
The aromatic portion of the species synthesized by the method of the invention is generally oxidized to the corresponding quinone. The phenol can be oxidized directly to the quinone or, alternatively, it can first be converted to the corresponding hydroquinone and oxidized to the quinone. An array of reagents and reaction conditions are known that oxidize phenols to quinones, *see*, for example, Trost BM *et al.* COMPREHENSIVE ORGANIC SYNTHESIS: OXIDATION, Pergamon Press, 1992.

In a preferred embodiment, the oxidant comprises a transition metal chelate. The chelate is preferably present in the reaction mixture in an amount from about 0.1 mol % to about 10 mol %. In another preferred embodiment, the transition metal chelate is used in conjunction with an organic base, such as an amine. Presently preferred amines are the trialkyl amines, such as triethylamine. In another preferred embodiment, the transition metal chelate is Co(salen). The chelate can be a heterogeneous or homogeneous oxidant. In a preferred embodiment, the chelate is a supported reagent.

The alkene component of the reaction pathway of the invention can be prepared by any of a number of methods known in the art for assembling such compounds. In an exemplary art-recognized method, an allylsulfone moiety is coupled to an allyl chloride to form the desired polyene (*see, e.g.*, Lipshutz *et al.*, *J. Am. Chem. Soc.* 121: 11664-11673 (1999)). The sulfone moiety serves as a control element for the synthesis of the polyprenoidal derivatives. The use of the sulfone derivatives allows for

the facile scale-up of the reactions assembling the polyprenoidal component of the ubiquinones and their analogues.

In a preferred embodiment, the compound according to Formula IV is produced by a method comprising contacting a compound according to Formula V:



(V)

with a compound according to Formula VI:

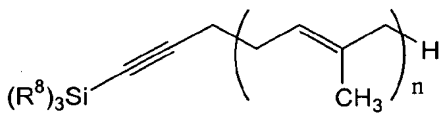
(VI)

in the presence of a base.

In Formula V, Y^1 is a leaving group, as discussed above. In a preferred embodiment, the leaving group is a halogen, more preferably a chloro group.

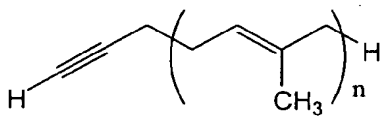
In Formula VI, R^8 is preferably substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroalkyl. Each of the R^8 groups is independently selected and they are the same or different.

The anion of a compound according to Formula VI, is contacted with a compound according to Formula V, thereby forming a compound according to Formula VII:



(VII).

The anion is formed *in situ* or, alternatively, it is formed prior to combining the constituents of the reaction. The anion is formed with an appropriate base, which is preferably an organolithium base. The compound according to Formula VII is subsequently desilylated to produce a compound according to Formula VIII:



(VIII).

The compound of Formula VIII is then carbometalated to produce a compound according to Formula III.

Alternate synthetic routes for use to convert the compounds of the invention to ubiquinones are provided in U.S. Patent No. 6,545,184 to Lipshutz et al.

The materials, methods and devices of the present invention are further illustrated by the examples which follow. These examples are offered to illustrate, but not to limit the claimed invention.

EXAMPLES

The following Examples provide representative synthetic procedures that are useful to practice the method of the invention. Example 1 sets forth a representative synthesis of a prenoidal species useful in practicing the present invention. Example 2 describes an alternate route for removing the TMS group from a TMS-protected alkyne, such as that prepared in Example 1. Example 3 sets forth a Ni mediated coupling of an alkyne and a representative aromatic moiety to provide a cross-coupled product. Example 4 sets forth an oxidation of a phenol prepared by a method of the invention to the corresponding quinone.

EXAMPLE 1

1.1 Preparation of Reagents

PCl_3 was refluxed for 3 h at 76°C while slowly purging with dry argon to expel HCl, distilled at atmospheric pressure and stored in a sealed container under argon until needed. DMF, 2-propanol and benzene were used as supplied from Fisher chemicals. Solanesol, purified by column chromatography on SiO_2 with 10% diethyl ether/petroleum ether, was dried azeotropically with toluene or benzene immediately prior to use. THF was distilled from Na/benzophenone ketyl prior to use. *n*-BuLi was obtained as a 2.5 M solution in hexanes from Aldrich and standardized by titration immediately prior to use. Ethanol was 200 proof, dehydrated, U.S.P. Punctilious grade. All other reagents were used as supplied by their respective vendors. Products were confirmed by ^{1}H NMR, IR, LREIMS and HR-EI or HR-CI Mass Spectrometry.

1.2 Chlorination of Solanesol

DMF (5.0 mL) was cooled to 0°C and PCl_3 (370 μL, 3.30 mmol) was added slowly such that the reaction warmed but was never hot to the touch. Stirring was suspended, the ice bath removed and the reaction let stand until a solid had formed (1.25

h). The reaction was recooled to 0°C, stirring resumed and solanesol (2.97 g, 4.7 mmol) in 5 mL benzene was added with benzene (2 x 1 mL) to complete the transfer. The ice bath was removed after addition of solanesol and the reaction was monitored by TLC. After 0.5 h the reaction was carefully poured onto petroleum ether (30 mL) and saturated $NaHCO_3$ solution (30 mL) and ice. The layers were separated and the aqueous layer extracted with petroleum ether (3 x 10 mL), the combined organics washed once with saturated brine solution (20 mL) and dried over anhydrous $MgSO_4$. The product was concentrated to a clear brown oil via rotary evaporation and dried azeotropically with toluene (2 x 5 mL) prior to use in the next step.

1.3 Alkylation of Lithiated TMS-propyne

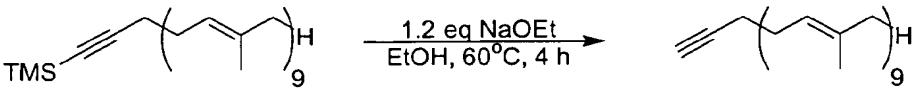
THF (20 mL) at -78 °C was charged with 1.26 mL *n*-BuLi (2.48 M in hexanes, 3.13 mmol) and after 5 min, 490 μ L TMS-propyne (355 mg, 3.17 mmol) were added. After 1.5 h at -78 °C, the reaction was warmed to -20 °C for 0.75 h then recooled to -50 °C.. Crude chloride (2.10 g, 3.17 mmol) dissolved in 10 mL THF was cooled to -50 °C and added slowly via cold cannula. The reaction was warmed to rt over 3.5 h and quenched by addition of 1 mL saturated NH_4Cl solution, and the brown mixture concentrated via rotary evaporation to a brown oil. The residue was dissolved in 20 mL water and 20 mL petroleum ether and the layers separated. The aqueous phase was extracted 3 X 10 mL hexanes and the combined organics washed with 20 mL brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash chromatography 5% CH_2Cl_2/petroleum ether gave the product as a clear, colorless oil which solidified upon standing 1.91g (83 %).

1.4 Deprotection of the TMS-protected Alkyne

The crude material from the alkylation was dried azeotropically with benzene (3 x 5 mL), after which ethanol (20 mL) and 2-propanol (7 mL) were added. The mixture was warmed to 35°C to dissolve the crude alkyne. K_2CO_3 (850 mg, 6.2 mmol) was added. After stirring overnight, the mixture was poured onto water (50 mL) and diethyl ether (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organics were washed once with saturated brine solution (10 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. Column

chromatography with 1% diethyl ether/petroleum ether yielded 1.39 g of a pale yellow oil (59% based on *n*-BuLi).

EXAMPLE 2



2.1 Reagents

Ethanol was obtained from Rossville, Gold Shield U.S.P. grade 95% and stored in a sealed metal container. Sodium metal was stored under toluene and cut fresh just prior to addition to ethanol. TMS-Alkyne was purified by column chromatography and was a clear oil of >95% purity by ^{1}H NMR.

2.1a Preparation of sodium ethoxide

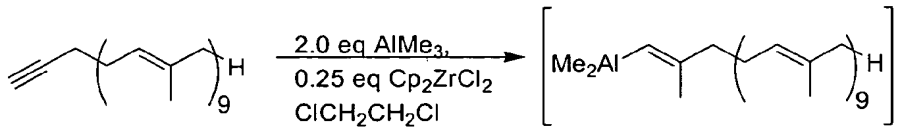
Ethanol (10 mL, 95%) was placed in an open container with a slow stream of argon passing over it, sodium (53 mg, 2.31 mmol) was carefully added and allowed to dissolve. The theoretical concentration of NaOEt was 0.154 M.

2.2 Removal of TMS Group

TMS-Alkyne (256 mg, 0.353 mmol) in a 10 mL round bottom flask with a stir bar was charged with 2.8 mL of the sodium ethoxide solution (0.425 mmol, 0.15 M in NaOEt) and a reflux condenser attached. The biphasic solution was heated to 60-65 °C in a oil bath for 4 h. The reaction was poured onto 10 mL of deionized H_2O and 10 mL of petroleum ether, the layers were separated, the aqueous layer extracted three times with 10 mL petroleum ether and the combined organics washed once with 10 mL saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Chromatography of the residue with 10 % CH_2Cl_2/petroleum ether gave 228 mg of a clear oil (99%). Purity was confirmed by ^{1}H NMR as >95% pure.

EXAMPLE 3

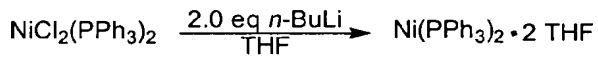
3.1 Carboalumination of alkyne 1



1 2

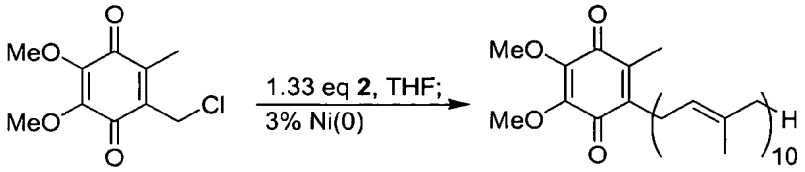
Cp_2ZrCl_2 (74 mg, 0.25 mmol) and $AlMe_3$ (0.5 mL, 2.0 M in hexanes, 1.0 mmol) were combined and about 90% of the solvent was removed *in vacuo*. The gray-white residue was then dissolved in $ClCH_2CH_2Cl$ (DCE) (0.5 mL) giving a pale yellow solution. Alkyne (325 mg, 0.5 mmol) in DCE (0.25 mL) was added via cannula (exothermic) followed by washings with DCE (2 x 0.125 mL) to complete the transfer. After 11 h at room temperature, the solvent was completely removed from the heterogeneous yellow mixture *in vacuo*. The residue was triturated hexanes (3 x 3 mL) and the hexanes removed *in vacuo* to remove all traces of DCE. To the heterogeneous yellow mixture was then added hexanes (2 mL) and the resulting supernatant was cannulated away from the residual Zr salts. The salts were washed twice with hexanes (2 x 1 mL) which were combined with the original washing. The combined clear yellow hexane solution containing the vinylalane was then concentrated *in vacuo* and the residue dissolved in 0.5 mL THF (exothermic) in preparation for the cross-coupling reaction.

3.2 Preparation of the Ni(0) catalyst.



In an oven dried 5 mL round bottomed flask containing a stir bar, cooled and purged with argon, was added $NiCl_2(PPh_3)_2$ (19.6 mg, 0.03 mmol) and the vessel was purged with argon for 2 minutes. THF (0.5 mL) was then added and slow stirring commenced. Slow addition of *n*-BuLi (0.026 mL, 0.058 mmol) gave a blood-red/black heterogeneous solution which was allowed to stir for 2 min prior to using it in the coupling reaction.

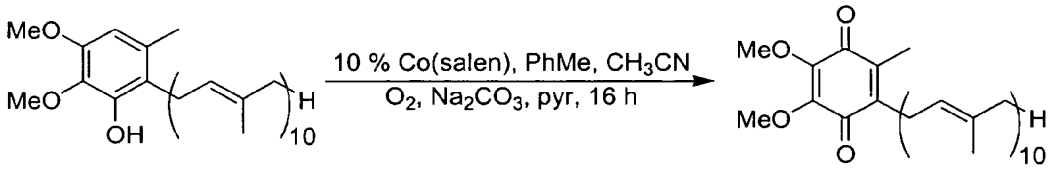
3.3 Coupling of chloromethylated quinone with vinylalane



Chloromethylated quinone **F** (86 mg, 0.375 mmol) was dissolved in THF (0.4 mL) and was cannulated into a solution of vinylalane **2**. Two 0.3 mL washings of THF were used to complete the transfer of **F**. The Ni(0) catalyst solution (0.188 mL, 0.011 mmol, 3 mol %) was added at room temperature *via* syringe. The solution was then protected from light and allowed to stir at rt for more than about 4h. The reaction was quenched by the addition of EtOAc (10 mL) and 1 M HCl (20 drops). The mixture was stirred for 10 min to break up the aluminum salts (alternatively, a solution containing 0.3 g citric acid/mL water may be used to quench the reaction, followed by extraction with $CHCl_3$). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10mL). The organics were combined, washed once with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting yellow oil was subjected to column chromatography (10% EtOAc/petroleum ether) to give 291 mg of CoQ_{10}, identical in all respects with an authentic sample.

EXAMPLE 4

4.1 Synthesis



In a clean 25 mL round bottom flask and stir bar (note: not oven dried and not under argon) the phenol (99.4 mg, 0.117 mmol) was dissolved in toluene (1 mL) and Na_2CO_3 (36.4 mg, 0.37 mmol) and pyridine (1 μL, 0.012 mmol) were added. Co(salen) (1.9 mg, 0.006 mmol) was then added as a red-purple solid and the reaction vessel was purged with ~0.5 liter O_2 and held under an atmosphere of oxygen for the full reaction period. CH_3CN (150 μL) was then added to assist in solubilizing the cobalt complex. After 16 h, the reaction mixture was filtered and the supernatant was concentrated *in vacuo* and then chromatographed (5% EtOAc/petroleum ether) giving 68.6 mg of a red oil

which solidified to a orange solid upon standing (69%). The identity of the product was confirmed by ^{1}H NMR, mp, HRMS and comparison to authentic sample by HPLC. Purity was established by HPLC at 98%.

TLC: R_f = 0.22(10 %EtOAc/petroleum ether);

mp = 44.8-45.9 °C;

^{1}H NMR (400MHz, $CDCl_3$) δ 5.08 (m, 7H), 4.91 (t, J = 7.3Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.15 (d, J = 7.2Hz, 2H), 2.05-1.93 (m, 31H), 171 (s, 3H), 1.65 (s,3H), 1.57 (s, 21H);

LREIMS 864(15, M^+), 235(41), 197(96), 135(12), 121(12), 107(12), 95(18), 93(18), 80(58), 68(100);

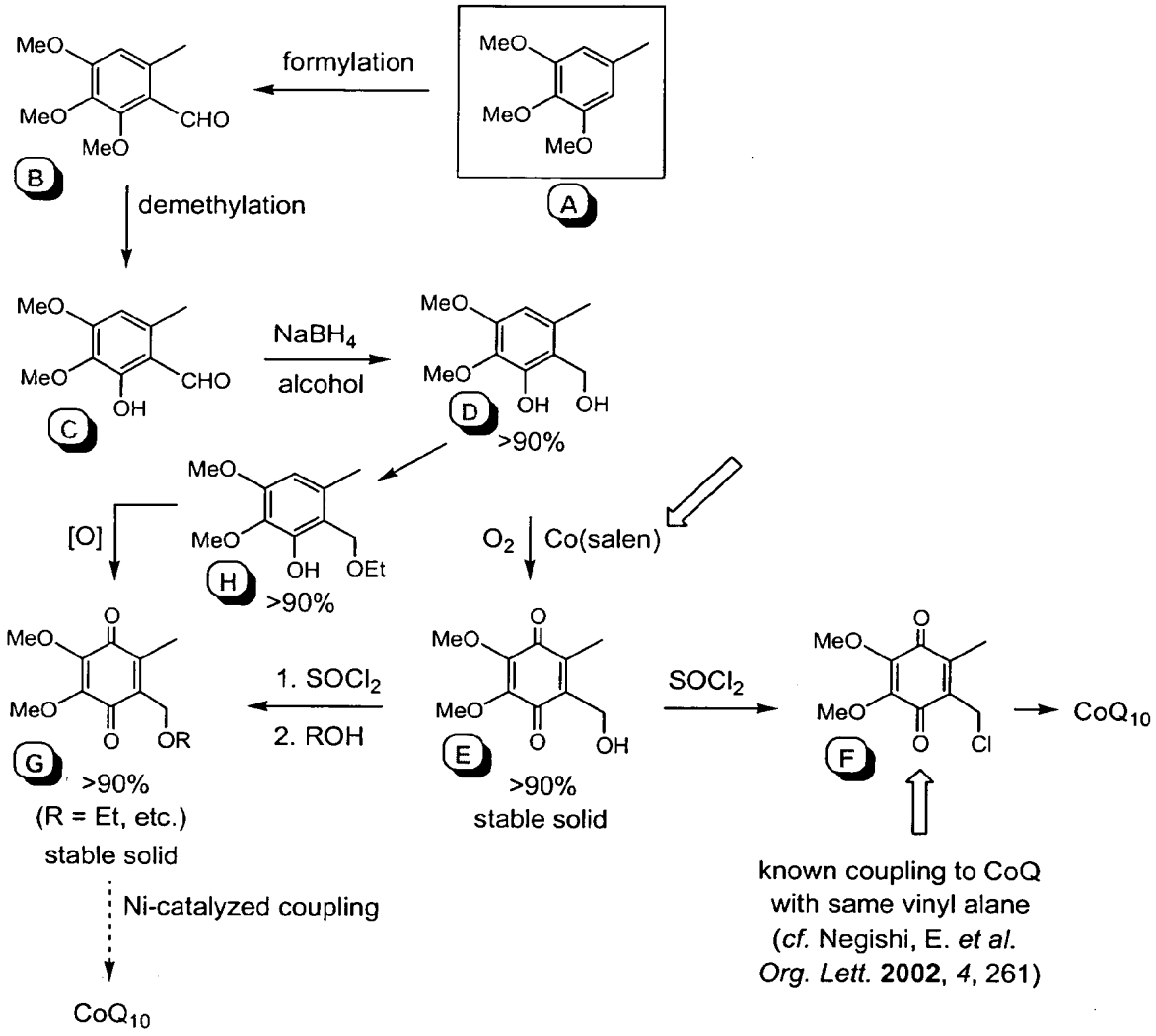
HREIMS calculated for $C_{59}H_{90}O_4$, 862.6839, found 862.6864.

PRACTICAL, COST-EFFECTIVE SYNTHESIS OF CoQ_{10}

ABSTRACT OF THE DISCLOSURE

The present invention provides a convergent method for the synthesis of ubiquinones and ubiquinone analogues. Also provided are precursors of ubiquinones and their analogues that are useful in the methods of the invention.

FIG. 1


MeO
MeO
MeO
CHO
formylation
B
A
demethylation
OH
NaBH4
alcohol
OH
OH
D
>90%
C
[O]
OEt
H
>90%
O2
Co(salen)
1. SOCl2
2. ROH
OR
G
>90%
(R = Et, etc.)
stable solid
Ni-catalyzed coupling
CoQ10
E
>90%
stable solid
SOCl2
Cl
F
CoQ10
known coupling to CoQ
with same vinyl alane
(cf. Negishi, E. et al.
Org. Lett. 2002, 4, 261)

Application Data Sheet

Application Information

Application number::	
Filing Date::	
Application Type::	Provisional
Subject Matter::	Utility
Suggested classification::	
Suggested Group Art Unit::	
CD-ROM or CD-R??::	
Number of CD disks::	
Number of copies of CDs::	
Sequence Submission::	
Computer Readable Form (CRF)?::	
Number of copies of CRF::	
Title::	PRACTICAL, COST-EFFECTIVE SYNTHESIS OF CoQ_{10}
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Request for Early Publication::	No
Request for Non-Publication::	No
Suggested Drawing Figure::	
Total Drawing Sheets::	1
Small Entity?::	Yes
Latin name::	
Variety denomination name::	
Petition included?::	No
Petition Type::	
Licensed US Govt. Agency::	
Contract or Grant Numbers One::	
Secrecy Order in Parent Appl.::	No

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Correspondence Customer Number:: 20350

Representative Information

Representative Customer Number:: 20350

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::

Foreign Priority Information

Country::	Application number::	Filing Date::

Assignee Information

Assignee Name::

Street of mailing address::

City of mailing address::

State or Province of mailing address::

Country of mailing address::

Postal or Zip Code of mailing address::